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Report

Diagnostic value of contrast-enhanced computed tomography for diagnosing the intraductal component of breast cancer

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Summary

Background: It is important to reduce local residual cancer to avoid local recurrence after breast conserving treatment. We therefore tried to detect the intraductal components and small invasive foci of breast cancers by contrast-enhanced helical computed tomography (CE-CT). *Methods:* In 122 women whose breasts were examined by CE-CT preoperatively, intraductal spread detected on ultrasound (US), mammography (MMG), and CE-CT, and extensive intraductal components (EICs) detected by histological examination were analyzed for correlations among the extent and subtypes of intraductal components, and deviations in tumor size. *Results:* EICs were present in 44 patients. The sensitivities of EIC detection by US, MMG, and CE-CT were 35%, 61%, and 88%, respectively, and the corresponding specificities were 83%, 86%, and 79%, respectively. The sensitivities of detecting EIC and small invasive foci were 34%, 57%, and 91%, respectively. In 5 patients, EIC could only be visualized by CE-CT. The median deviation of the size of intraductal spread revealed by CE-CT from pathological EIC was 0.0 cm (range + 3.0 to – 1.7 cm). *Conclusions:* CE-CT is useful for visualizing intraductal spread and small invasive foci of breast cancer.

Introduction

The preoperative identification of an extensive intraductal component (EIC) in invasive ductal carcinoma of the breast is an important factor determining the extent of breast resection required. Although mammography (MMG) and ultrasonography (US) are still the main tools used for the detection and diagnosis of breast cancer, they often underestimate the extent of the tumor. The sensitivity of MMG for detection of EIC has been reported to be 41%–83% [1–4]. MMG is of little value in cases without microcalcifications, since such microcalcifications are the only indication of EIC using this method, and multifocality is often undetected [5–7]. Some institutions have reported excellent visualization of EIC by US [2, 8], although the effectiveness of US seems to depend on the case examined, the investigator's skill, and the spatial resolution of the machine. In recent years, magnetic resonance imaging (MRI) has yielded additional information on the extent of invasion and intraductal spreading of breast cancer but has not been adopted in routine clinical practice because of its high cost and complexity.

Although Chang et al. have had significant success in detecting small cancers using contrast-enhanced computed tomography (CT) [9], the utility of this technique has not been corroborated be-

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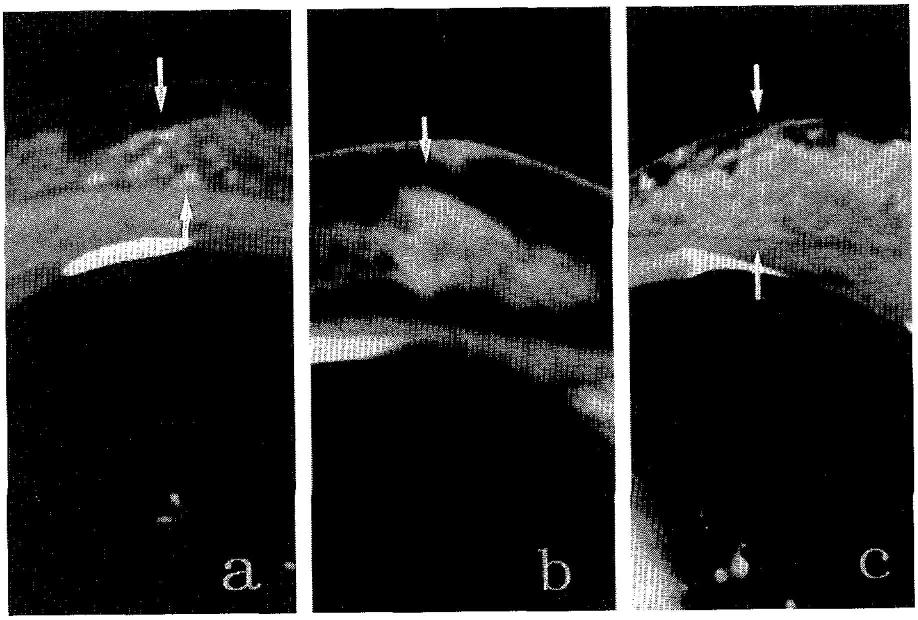

Figure 1. (a) An example of strong nodular enhancement in breast tissue detected by CE-CT. (b) Moderate enhancement. (c) Weak enhancement.

cause of the high radiation exposure and long scan time involved. On the other hand, improvements in helical CT technology have brought about the possibility of using it as a new technique for the diagnosis of breast cancer. Helical CT has several advantages over conventional CT, since it can obtain images without a gap between slices, and has a more rapid scan time with lower radiation exposure [10]. Helical CT also has a higher spatial resolution and is less expensive than MRI. Pilot examinations of contrast-enhanced helical CT (CE-CT) have suggested its usefulness for detecting EIC [11].

The objectives of the present study were to determine whether CE-CT is more useful for detecting EIC and small invasive foci of breast cancer than US or MMG.

Materials and methods

Patients

Between November 1995 and May 1997, 514 women in whom MMG or US of the breast indicated breast carcinoma were admitted to the National Cancer Center Hospital for surgical treatment. The indications for CE-CT were as follows: 1) patients in whom MMG and/or US findings suggested widespread intraductal components (WSIC), as defined later (58 patients), 2) patients fulfilling our criteria for breast-conserving surgery ($T \leq 3$ cm, N0 and absence of multiple tumors and/or diffuse microcalcifications on MMG) (64 patients). A total of 122 women were evaluated preoperatively by CE-CT.

Imaging examinations

For mammographic examination, a Mammomat 3 (Siemens, Germany) was used. In addition to standard oblique and cranio-caudal projections, cranio-caudal or medio-lateral spot views (5 cm in diameter) without magnification were obtained in most cases. Whole-breast US was performed using a EUB-515 (Hitachi, Japan) with a 7.5-MHz transducer.

Helical CT scanning was performed using an X-Vigor (Toshiba, Japan) at 300 mA. The patients underwent one single spiral acquisition during deep inspiratory apnea for up to 30 s in the suspine position. The first step was identification of the main tumor by a non-contrast-enhanced CT scan from the cranial end of the sternum to the inframammary fold. Subsequently, enhanced zoomed scanning was planned from 30 mm above to 30 mm below the main tumor with a collimation of 2 mm and a pitch of 2 to 3 mm. One hundred milliliters of non-ionic contrast material (300 mg I/g) was injected at a rate of 2 ml/s. The time between the administration of the bolus injection of contrast material and the initiation of scanning was 60 s. The reconstruction interval was 2 mm.

MMG and CE-CT imaging studies were evaluated prospectively by two radiologists (K.M. and N.U.), and US images were evaluated by another radiologist (H.M.). WSIC positivity was defined according to the imaging data as follows: 1) microcalcifications beyond the tumor shadow or clustered malignant calcifications without a tumor shadow on MMG [3], 2) dilated hypoechoic ducts adjacent to the tumor on US [12] and 3) spotty nodular enhancements to the same intensity as the main tumor on CE-CT scan. When these findings were limited to within 10 mm of the main tumor, we considered them to be WSIC-negative. We measured the extent of microcalcifications evident on MMG, dilated ducts on US, and spotty nodular enhancements on CE-CT to determine the extent of WSIC. Comparing all CE-CT images showing positive WSIC, the intensity of WSIC enhancement on CE-CT was classified into one of the three grades: weak, moderate, or strong (Figure 1).

Histopathology

Surgical specimens were sectioned at about 7~10 mm intervals in a transverse direction. Pathology reports were reviewed to obtain data on tumor size, the presence of an EIC, and the subtype of the intraductal component. EIC was defined according to Schnitt [13]. In this series, one case with widespread lobular carcinoma *in situ* (LCIS) was included as EIC. Histological grades determined as reported previously [14] were evaluated separately in the invasive and intraductal components. Histologic subtypes of the intraductal components were categorized as either comedo or non-comedo type including cribriform, solid, papillary, and micropapillary type, depending on the predominant type.

Statistical methods

The chi-square test was used for statistical analysis, and differences at $P < 0.05$ were considered significant.

Results

Patient characteristics

The clinical and pathological characteristics of the patients are shown in Table 1. Of the 64 candidates for BCT, 27 actually chose the procedure, and the others chose mastectomy because of concern about radiotherapy and/or local recurrence. Among the 27 resected specimens obtained by BCT, a positive surgical margin was histologically confirmed in only one patient, who was the first candidate considered

Table 1. Patient characteristics

Clinical features	Total no. of patients
Age (yr)	
≤ 34	7
35~49	42
50~65	53
≥ 66	20
Tumor size on palpation	
T1	46
T2	64
T3	6
Post-biopsy status	6
Histology	
IDC	88
IDC with PIC	10
DCIS	5
ILC	5
Medullary	4
Paget	1
Benign tumor	9
EIC	
EIC (+)	44
EIC (−)	78

T1: tumor not more than 2 cm in greatest dimension, T2: tumor more than 2 cm but not more than 5 cm in greatest dimension, T3: tumor more than 5 cm in greatest dimension, IDC: invasive ductal carcinoma, IDC with PIC: invasive ductal carcinoma with a predominant intraductal component, ILC: invasive lobular carcinoma, DCIS: ductal carcinoma *in situ*, EIC: extensive intraductal component.

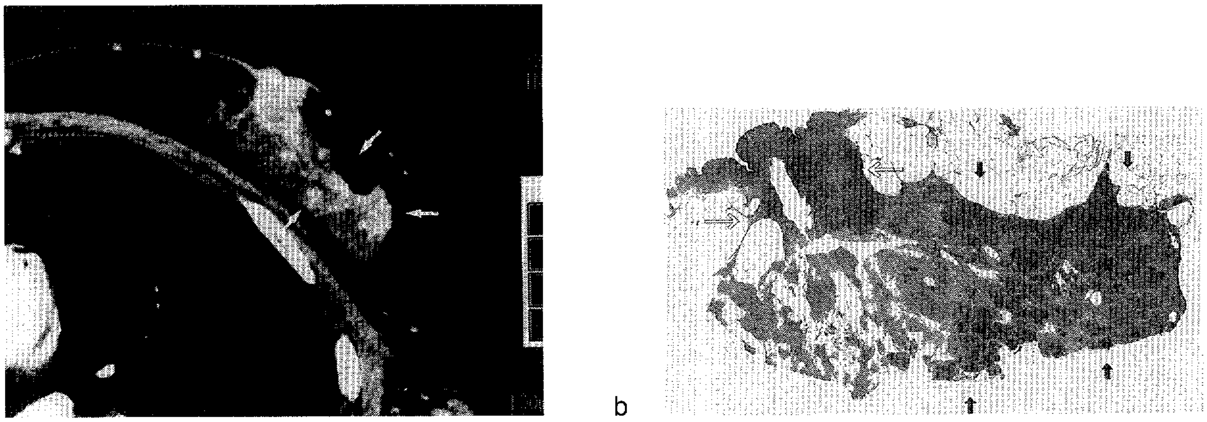

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Figure 2. Invasive ductal carcinoma with EIC. MMCT and US showed the presence of a tumour about 2 cm in diameter just beneath the nipple. (a) CE-CT visualised numerous tiny nodules in a 7 cm region surrounding the area of tumorous enhancement beneath the nipple. (b) Low magnification of the resected specimen. The main tumor is shown as ⇑ and EIC (↑) can be seen in the right half of the specimen. (H & E, original magnification × 2)

for BCT after CE-CT. EIC was present in 44 patients.

Sensitivity and specificity

The sensitivity for detecting EIC was 35% for US, 61% for MMG, and 88% for CE-CT (Table 2). The specificity for detecting EIC was 83% for US, 86% for MMG, and 79% for CE-CT. The sensitivity for detecting cancerous lesions including EIC and small invasive foci was 34% for US, 57% for MMG, and 91% for CE-CT. The sensitivities for detecting EIC and cancerous lesions were significantly higher for CE-CT than for US and MMG. EIC was detected preoperatively by CE-CT alone in five patients. One example is illustrated in Figure 2. The sensitivities and specificities are shown separately in Tables 3 and 4 for two groups: one composed of 58 patients in whom MMG or US findings suggested a WSIC, and the other of 64 patients fulfilling the criteria for breast-conserving surgery.

False positive detection of EIC

Pathologically, 10 out of 16 cases that were false positive for EIC by CE-CT were small invasive lesions. The reasons for false positive detection of EIC in the remaining 6 tumors by CE-CT were explained as follows: 1) Spotty enhancement was identified as atypical ductal hyperplasia (3 patients) and intraductal papilloma (1 patient). 2) A diffusely enhanced area was pathologically proven to be interlobular fibrosis (1 patient). 3) Bridging lesions between multifocal cancers were visualized by CE-CT

Table 2. Sensitivity and specificity of each imaging modality

	Sensitivity in visualizing EIC		Sensitivity in visualizing EIC or small invasive foci		Specificity in visualizing EIC	
	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n
US	35 (21–51)	43*	34 (22–48)	53*	83 (73–91)	78
MMG	61 (45–76)	44	57 (43–71)	54	86 (76–93)	78
CE-CT	88 (75–96)	44	91 (80–97)	54	79 (69–88)	78

US: ultrasonography, MMG: mammography, CE-CT: contrast-enhanced computed tomography, EIC: extensive intraductal component, CI: confidence interval.

* US was not performed in one patient with EIC after biopsy at another hospital.

Table 3. Sensitivity and specificity of each imaging modality in candidates for breast-conserving surgery

	Sensitivity in visualizing EIC		Sensitivity in visualizing EIC or small invasive foci		Specificity in visualizing EIC or small invasive foci	
	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n
US	11 (0–48)	9*	9 (0–41)	11*	100 (92–100)	45
MMG	10 (0–44)	10	8 (0–38)	12	100 (92–100)	45
CE-CT	70 (35–93)	10	75 (43–95)	12	96 (85–100)	45

US: ultrasonography, MMG: mammography, CE-CT: contrast-enhanced computed tomography, EIC: extensive intraductal component, CI: confidence interval.
* US was not performed in one patient with EIC after biopsy at another hospital.

Table 4. Sensitivity and specificity of each imaging modality in patients in whom US or MMG findings suggested a WSIC

	Sensitivity in visualizing EIC		Sensitivity in visualizing EIC or small invasive foci		Specificity in visualizing EIC or small invasive foci	
	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n
US	38 (22–56)	34	39 (24–56)	41	43 (18–71)	14
MMG	74 (56–87)	34	69 (53–82)	42	62 (32–86)	13
CE-CT	94 (80–99)	34	95 (84–99)	42	71 (42–92)	14

US: ultrasonography, MMG: mammography, WSIC: widespread intraductal component, CE-CT: contrast-enhanced computed tomography, EIC: extensive intraductal component, CI: confidence interval.

as well as by US and MMG, but these were not identified by histopathology. This might have been due to interlobular fibrosis (1 patient).

False negative detection of EIC

False negative results obtained by CE-CT were explainable in a similar manner: 1) Bridging lesions between multifocal cancers were not detected by CE-CT in 3 patients. 2) EIC was visualized as a peripheral irregularity of the main tumor by CE-CT in 2 patients.

Subtypes of intraductal components

Of the intraductal components examined, 17 were of the comedo type and 27 were of the non-comedo type. Fourteen (82%) comedo-type components

Table 5. Correlation between the subtype of the intraductal component and the grade of enhancement on CE-CT

Grade of enhancement	Subtype of intraductal component			Histological grade		
	Comedo	Non-comedo		1 + 2	3	
Strong	9	8	a	11	6	b
Moderate	8	12		16	4	
Weak	0	2		2	0	

a: NS, b: NS.

Table 6. Differences in the size of cancerous extension determined by MMG and CE-CT and sizes determined histologically

Deviation from pathological size (cm)	MMG	CE-CT
5.1 –	1	0
3.1 – 5.0	3	1
2.1 – 3.0	5	1
1.1 – 2.0	4	6
0.1 – 1.0	24	28
0	5	8
Not diagnosed as cancer	2	0

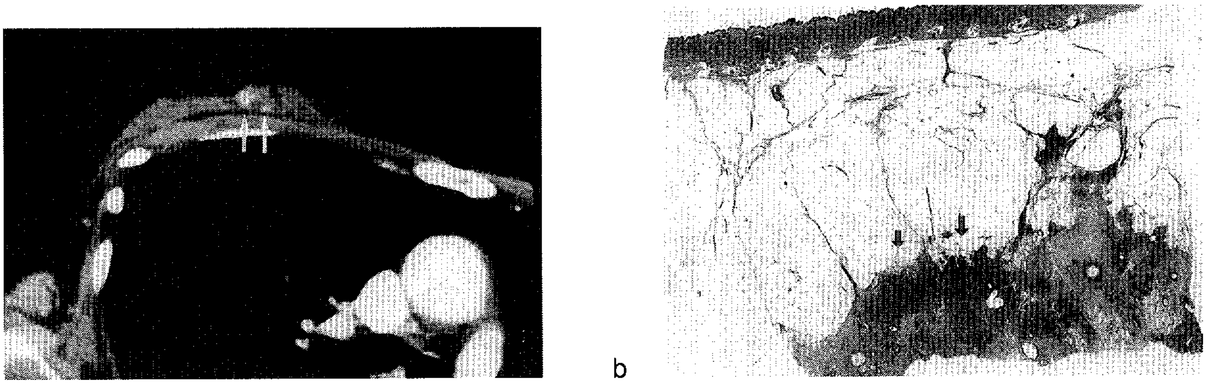

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Figure 3. This patient had a right breast mass 3 cm in a diameter in the inner lower quadrant. MMG revealed a spiculated mass without malignant calcifications, and US demonstrated an irregulary shaped hypoechoic mass indicating cancer. (a) CE-CT revealed several nodular enhancement up to 0.4 cm in diameters around the main tumor. This slice was taken 2.4 cm cranial to the main tumor. (b) Low magnification of the resected specimen about 2.4 cm cranial to the main tumor. Several small invasive foci up to 0.3 cm in diameter can be seen (↑). (H & E, original magnification × 2)

and 12 (44%) non-comedo-type components were visualized as microcalcifications on MMG. With US, 7 comedo and 7 non-comedo-type components were identified on the basis of dilated hypoechoic ducts. All comedo components and 81% (22/27) of non-comedo components were visualized by CE-CT. The intensity of enhancement on CE-CT was not related to the subtype of these intraductal components (Table 5). Intraductal components of higher histological grade tended to show stronger enhancement.

Differences between sizes of WSIC and EIC

Differences between the sizes of the WSIC visualized by MMG and CE-CT and the sizes of EIC determined histologically are shown in Table 6. The median deviation of WSIC determined by CE-CT from pathological EIC was 0 cm (range +3.0 to −1.7 cm). CE-CT demonstrated EIC more accurately than MMG.

EIC visualized only by CE-CT

The EIC visualized only by CE-CT was of the comedo type in 2 patients and the non-comedo type in 2. One further *in situ* component was visualized only by CE-CT in a patient with invasive carcinoma with a predominant intraductal component associated with lobular carcinoma *in situ*. Not only *in situ* components but also multiple small invasive foci of up to 0.3 cm surrounding the main tumor in one case were visualized only by CE-CT (Figure 3).

Discussion

In recent years, breast-conserving treatment (BCT) has come to be recognized as a standard treatment option in selected patients. However, even if radiotherapy is followed by BCT, local recurrence occurs in 5–20% of patients [15–17]. Some reports have indicated that survival after salvage mastectomy for treatment of local recurrences is worse than that obtained if local failure does not occur [18, 19]. Moreover, local failure causes severe psychological distress due to both the recurrence and the need for a second operation. It is considered that the presence of an EIC itself is not a contraindication for BCT, although resection of cancerous lesions as far as possible including the EIC is important for preventing local failure [20, 21]. Therefore, our standpoint when performing BCT is to detect EIC and small invasive lesions accurately before surgery, and to remove them all.

In this study, the sensitivity of CE-CT for detection of EIC was 88%, which was significantly higher than that of US and MMG. Among 5 patients with false negative results, 3 with multifocal tumors were ineligible for breast conserving surgery because of the presence of multiple tumors [22]. Two patients with EIC which were visualized as a peripheral irregularity of the main tumor on CE-CT could be treated by wide excision with a cancer-free margin. From the viewpoint of BCT, there were few false negative cases. In 95% (42/44), differences between the extent of the WSIC estimated by CE-CT and the pathological extent of the cancer were less than 2 cm. Thus CE-CT gives additional information when planning BCT. In particular, CE-CT was preferable to MMG for women with dense breasts.

When CE-CT demonstrates findings of WSIC within the same quadrant, we have recently begun to reconstruct a front view of the breast, which is useful for determining the optimal extent of resection. When CE-CT demonstrates no sign of WSIC, wide excision may be the most appropriate procedure.

During follow-up after BCT, CE-CT is also sensitive for diagnosing local recurrence of breast cancer, even in non-palpable lesions [23]. In this situation, the sensitivity of breast CT is 91% and its specificity is 85%.

The basic theory behind CE-CT is similar to the concept of contrast-enhanced MRI [24]. Angiogenesis has been demonstrated to be associated with a wide variety of breast cancers, including strictly defined intraductal cancers [25]. Breast cancers have been shown to have increased capillary permeability and an enlarged interstitial space [26]. Enhanced MRI seems to function as a means of estimating blood flow [27]. In the present series of patients, capillary vessels were noticed in the immature or myxoid fibrous stromal tissue around the intraductal cancerous lesions. As it is impossible to recognize each of the involved ducts by CE-CT, we considered EIC and these immature stromal components together as one enhanced nodule.

A recent study has shown that the intensity of enhancement is correlated with the number of blood vessels in pathologic specimens [28]. Folkman et al. demonstrated in mice that angiogenic activity first appears in a subset of a few hyperplastic islets, and that this is an important step in carcinogenesis [29]. It is reasonable to expect that fibrocystic changes such as ductal hyperplasia would be enhanced weakly, and that this would be enough to distinguish them from cancerous lesions. However, it was difficult to distinguish intraductal components from small invasive components on CE-CT, because their specific morphologic enhancement patterns were not demonstrated.

It is well known that ductal carcinomas with intraductal components of the comedo variety are more aggressive and more likely to recur than their non-comedo-type counterparts [16]. Local recurrence after BCT occurs especially often in comedo carcinomas even though the patients receive postoperative radiotherapy. Fortunately, most comedo-type carcinomas are demonstrable by microcalcifications [3]. However, in two patients with comedo-type tumors in this study, no microcalcifications were evident. CE-CT was helpful for identifying non-calcified comedo-type and non-comedo-type carcinomas.

Many reports have documented the role of MRI in the detection and management of breast diseases [5, 7]. We initially tried enhanced MRI for detecting WSIC, but found that the spatial resolution was unsatisfactory and that scanning took about 40 min. Subsequently, we tried CE-CT and obtained small enhanced images with good spatial resolution. This enabled us to take subsequent scans within 5 min [11]. Image quality depends greatly on the performance of the machine employed. In most previous studies, patients were examined in the prone position to minimize motion of the breast during breathing. On the other hand, CE-CT breast images obtained in the supine position used during surgery would be a great advantage.

In conclusion, CE-CT of the breast is useful for estimating the extent of intraductal components and small invasive foci in order to determine the extent of resection required during BCT.

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